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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,770	06/28/2007	Yoshihide Hayashizaki	1794-0190PUS1	5639

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EXAMINER	
KINGAN, TIMOTHY G	

ART UNIT	PAPER NUMBER
1797	

NOTIFICATION DATE	DELIVERY MODE
10/14/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/594,770	HAYASHIZAKI ET AL.	
	Examiner	Art Unit	
	TIMOTHY G. KINGAN	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19 and 24-26* is/are rejected.

7)☐ Claim(s) *20-23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03/02/2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/29/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claims 1-6, 9, 11-15 and 17-18** are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Y. Hayashizaki and I. Tanihata, WIPO published patent application WO 2002/068952. Examiner relies on U.S. equivalent, U.S. Patent Application Publication 2004/0113606 (herein after Hayashizaki).

For Claims 1-6, 9, 11-15 and 18 Hayashizaki teaches performing laser ablation of polymers (biosamples or smear sample), by the ultra-short pulse laser beams, the polymers atomized to each of the atoms that constitute the polymer, with the atomized atoms ionized into univalent ions followed by quantitative analysis of the atomic ions generated by the ionization [0014]. Further, Hayashizaki teaches the polymers may be added with (labeled by) an elemental label (directly or indirectly labeling a substance) [0025], such label may be a stable isotopic label [0030] and that analysis may be performed on various kinds of polymers attached with elemental labels including DNA (nucleic acid), protein and PNA ([0013], [0135]) with use of a quadrupole mass spectrograph [0045], such as a time-of-flight mass spectrograph (analysis by mass spectrometry with a time-of-flight method). Hayashizaki also teaches that a probe comprising a nucleotide may be labeled with a stable isotope [0058], hybridized with

target nucleic acid and laser ablated for analysis [0059] (labeled substance is bonded by hybridization). Further Hayashizaki teaches that a plurality of probes may be labeled with different elements and simultaneously hybridized with the target to achieve multi-channeling capability when used with a DNA microarray (multi-channeling is conducted).

For Claim 17, Hayashizaki teaches laser beams of pulse duration of 1 femto second or more and 1 pico second or less, and a peak power of 1 gigawatt or more and 10 gigawatt or less [0032].

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. **Claims 7 and 10** are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki as applied to claim 2 above, and further in view of Y. Hayashizaki,

WIPO published patent application WO 2002/044195. Examiner relies on U.S. equivalent, U.S. Patent Application Publication 2004/0115665 (herein after Hayashizaki '665).

For Claim 7, Hayashizaki does not teach use of labeled aptamers in analyzing molecules in a biosample. However, Hayashizaki teaches application of laser ablation to analysis of protein [0013], and Hayashizaki '665 teaches use of aptamers in analysis of proteins, such as thrombin [0005], such analysis comprising fixing of aptamer to a substrate/chip followed by binding of labeled ligand to said aptamer [0021]. From such teaching of binding of aptamer and labeled target, binding occurring in the solid phase, it would have been obvious to one of ordinary skill in the art, and with reasonable expectation of success, to label the aptamer for use in analysis of such binding event, in order to provide the opportunity to screen libraries in a selection process characteristic of aptamers.

For Claim 10, Hayashizaki does not teach use of a labeled substance bonded by antigen-antibody reaction. However, Hayashizaki does teach use of isotope-labeled protein in analysis of polymers [0135] and Hayashizaki '665 teaches that ligands may be detected by an antibody (protein) that specifically binds to the ligand [0068]. It would have been obvious to one of ordinary skill in the art, from the considerations on the use of proteins in labeling, according to Hayashizaki, and the specific types of proteins that may be employed in forming binding pairs, according to Hayashizaki '665, to use a labeled antibody for binding to its protein ligand in analysis, or the alternative labeling of

the ligand protein in a binding event comprising its antibody, in order to attain the advantages in quantitative analysis and resolution, as taught by Hayashizaki.

6. **Claim 8** is rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki as applied to claim 3 above, and further in view of F. de Sauvage et al., U.S. Patent Application Publication 2003/0215457 (herein after de Sauvage).

For Claim 8, Hayashizaki does not teach labeling nucleic acid by a TUNEL method. However, such method of labeling nucleic acid (and use of such labeled material in applications comprising in situ hybridizations) is known in the art. de Sauvage teaches nick-end labeling of nucleic acids (TUNEL method) for use in hybridization studies and detection of cells undergoing apoptosis using tissue microarrays [0330]. It would have been obvious to one of ordinary skill in the art to use TUNEL in labeling nucleic acids for use in hybridization studies in order to attain the advantage of use of a single method and label that may be applied in parallel to any number of target nucleic acids.

7. **Claim 16** is rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki as applied to claim 1 above, and further in view of K.M. Beck and D.S. Wunschel, U.S. Patent 6,680,477 (herein after Beck).

For Claim 16, Hayashizaki does not teach observing a biosample by a microscope at a position corresponding to the position of the ablated spot. However, such step is known in the art of imaging by mass spectrometry. Beck teaches a system

for focusing laser light for ionization in mass spectrometry coupled with a process for creating a correlated optical image of the ion desorption region of a sample (abstract), such system comprising a microscope objective for collecting light of an optical image of the sample receiving laser light for ionization, such image being recorded by a camera (col 7, lines 23-36) (imaging the position of a biosample corresponding to ablated spot). It would have been obvious to one of ordinary skill in the art to use the system comprising coupled ionization/imaging with a microscope objective of Beck with the method of Hayashizaki in order to provide data capable of analyzing the distribution of target molecules.

8. **Claims 19 and 24-26** are rejected under 35 U.S.C. 103(a) as being unpatentable over Hayashizaki in view of Beck.

For Claim 19, 25 and 26 Hayashizaki teaches an apparatus comprising an ultra-short pulse laser **20**, a focusing lens **22**, a target holder **14** and a quadrupole mass spectrometer **16** ([0083], Fig. 1) for performing ablation of polymers (biosamples or smear sample) with use of ultra-short pulse laser beams, the polymers atomized to each of the atoms that constitute the polymer, with the atomized atoms ionized into univalent ions followed by quantitative analysis of the atomic ions generated by the ionization [0014]. Hayashizaki does not teach a microscope unit for observing the shape of the biosample. However, such components for use in mass spectrometry are known in the art. Beck teaches a system for focusing laser light for ionization in mass spectrometry coupled with a process for creating a correlated optical image of the ion

desorption region of a sample (abstract), such system comprising a microscope objective for collecting light of an optical image of the sample receiving laser light for ionization, such image being recorded by a camera (col 7, lines 23-36) (imaging the position of a biosample corresponding to ablated spot by an image analysis apparatus). It would have been obvious to one of ordinary skill in the art to incorporate the ionization/imaging system, with a microscope objective, of Beck, with the laser and mass spectrometer of Hayashizaki in order to provide technology capable of analyzing the distribution of target molecules.

For Claim 24, Hayashizaki teaches laser beams of pulse duration of 1 femto second or more and 1 pico second or less, and a peak power of 1 gigawatt or more and 10 gigawatt or less [0032].

Allowable Subject Matter

9. **Claims 20-23** are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Hayashizaki and Beck do not teach use of an upright microscope with the objective on the upper surface of the biosample or an inverted microscope with irradiation by an ultra-short pulse duration laser from the upper surface of the sample. Rather, Beck places the objective of a microscope, and the source of laser light adjacent to the lower surface ([0083], Fig. 1). The prior art of record does not teach or fairly suggest arrangement, or provide motivation for a rearrangement of combined Hayashizaki and Beck, of an upright microscope at the upper surface of a

substrate holding a sample to be analyzed by laser light delivered from the lower surface. Such arrangements with upright or inverted microscope may offer advantages by making use of "off-the-shelf" components in assembly of molecular image analysis system.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY G. KINGAN whose telephone number is (571)270-3720. The examiner can normally be reached on Monday-Friday, 8:30 A.M. to 5:00 P.M., E.S.T.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TGK /Jill Warden/
Supervisory Patent Examiner, Art Unit 1797